Notes

Chelation- and Non-Chelation-Controlled Addition of 2-(Trimethylsilyl)thiazole to α-Amino Aldehydes: Stereoselective Synthesis of the β-Amino-α-hydroxy Aldehyde Intermediate for the Preparation of the Human Immunodeficiency Virus Proteinase Inhibitor Ro 31-8959

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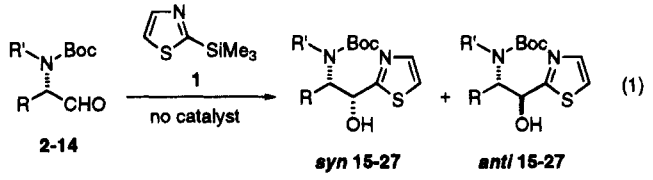
The addition of organometallic reagents to chiral *N*-protected α-amino aldehydes to give β-amino alcohols is receiving considerable attention as a key operation for the synthesis of biologically interesting compounds such as amino sugars,[1] sphingosines,[2] and peptidomimetics.[3,4] Control of the diastereoselectivity has been reported through the change of the metal and/or the presence of an added Lewis acid or chelating agent.[5] On the other hand, we have reported[6] some years ago a few yet significant examples of either *syn* or *anti* selective addition of 2-(trimethylsilyl)thiazole (2-TST, **1**) to some α-amino aldehydes containing a singly (R′ = H) or doubly (R′ ≠ H) protected nitrogen, respectively (eq 1). The



(1)

simplicity of this approach to achieve tunable stereoselectivity[7] and its synthetic potential and relevance with the preparation of a key intermediate[8] of the potent human immunodeficiency virus (HIV) proteinase inhibitor Ro 31-8959 prompt the disclosure of results of a more extensive investigation (Table 1).

Apart from the L-serine- and L-threonine-derived aldehydes **2** and **5**, the nitrogen-protecting groups employed for the other α-amino aldehydes were the benzyl (Bn) or its *p*-methoxy derivative (PMB)[9] and *tert*-butoxycarbonyl (Boc). It has been already pointed out[10] that the use of these protecting groups for nitrogen diprotection is quite convenient since they are of easy installation, tolerate various synthetic manipulations of the substrate, and are readily and selectively removable. The amino aldehydes **2**–**13** were synthesized either by partial reduction of amino esters with DIBALH or by complete reduction to alcohols with $LiAlH_4$ and Swern oxidation of the latter intermediates.[6,11,12] All compounds were used in crude form.[13] Reactions were carried out with 1.15 equiv of 2-TST (**1**) over the aldehyde under uniform conditions, and the diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixture after desilylative workup (Bu_4NF in THF). Stereochemical assignments for *syn* and *anti* amino alcohols were made by conversion to oxazolidinone derivatives as described.[6,14] The reaction of the aldehyde **14** with **1** was previously described by Wagner and Mollath.[15]

Previous and new results of Table 1 point out quite clearly the opposite diastereofacial selectivity of the addition of **1** to differentially *N*-protected amino aldehydes **2**–**14**. Invariably the reaction with singly protected compounds afforded the *syn* adducts as major products, whereas doubly protected derivatives gave the *anti* adducts predominantly. With one exception only, the levels of diastereoselectivity were high (ds 75–92%). Mixtures of *syn* and *anti* β-amino alcohols **15**–**27** were obtained in good yields (average of 70%) from which the individual pure isomers could be isolated in the same

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(1) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. Kiciak, K.; Jacobsson, U.; Golebiowski, A.; Jurczak, J. *Polish J. Chem.* **1994**, *68*, 199.

(2) For a recent survey of this area, see: Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469.

(3) Leading references: Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1992**, *33*, 7259. Konieczny, M. T.; Toma, P. H.; Cushman, M. *J. Org. Chem.* **1993**, *58*, 4619. Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 547.

(4) For a recent account on peptidomimetics, see: Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.

(5) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. Heneghan, M.; Procter, G. *Synlett* **1992**, 489. Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697. Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865. Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139 and references cited therein.

(6) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.

(7) The nitrogen-protecting group control on stereoselectivity has been successfully extended to the reduction of chiral α-amino ketones by metal hydrides (ref 31) and to the addition of 2-lithiothiazole to *N*-benzylnitrones derived from α-amino aldehydes; see: Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.* **1994**, 1731.

(8) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656.

(9) The use of the PMB protecting group provides a convenient alternative to Bn in synthetic methodology since the former can be removed under oxidative conditions and the latter under reductive conditions.

(10) Raczko, J.; Golebiowski, A.; Krajewski, J. W.; Gluzinski, P.; Jurczak, J. *Tetrahedron Lett.* **1990**, *31*, 3797.

(11) The quite popular aldehyde **2** was more conveniently prepared from the L-serine methyl ester via the reduction–oxidation route (see the Experimental Section) than via direct reduction as previously described (ref 30). In our hands, the latter procedure gave a mixture of aldehyde and alcohol. The same problem has been recently faced by other researchers; see: Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798.

(12) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181.

(13) The enantiomeric purity of some compounds (**2**, **10**, and **12**) was determined to be ≥95% ee by ^1H NMR analysis of the Mosher esters of the corresponding alcohols obtained by $NaBH_4$ reduction (see a detailed procedure in the Experimental Section). The enantiomeric purity of **8** (90% ee) had been previously determined in a similar way (ref 12).

(14) The mixture of diastereomeric β-amino alcohols was transformed (40% TFA/CH_2Cl_2, then Im_2CO, Et_3N, THF) into a mixture of oxazolidinones without altering the ratio of isomers. Oxazolidinones showed ^1H NMR coupling constants in the range 3.9–5.3 Hz for the *threo* isomers (from *syn* adducts) and 7.8–8.6 Hz for the *erythro* isomers (from *anti* adducts).

(15) Wagner, A.; Mollath, M. *Tetrahedron Lett.* **1993**, *34*, 619.

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Table 1. Addition of 2-(Trimethylsilyl)thiazole (1) to *N*-Boc-α-Amino Aldehydes[a] 2–14 (eq 1)

R	R′	aldehyde	product	yield,[b] %	*syn*:*anti*[c]
OCH_2	CMe_2	**2**	**15**	85	8:92[d,h]
$PhCH_2OCH_2$	H	**3**	**16**	60	80:20[d]
$TBDPSOCH_2$	H	**4**	**17**[i]	51	75:25[h]
(*R*)-OCHMe	CMe_2	**5**	**18**	68	15:85[d]
(*R*)-TBDPSOCHMe	H	**6**	**19**[i]	60	78:22[h]
Ph	$PhCH_2$	**7**	**20**	67	40:60[h]
Ph	H	**8**	**21**	70	88:12[e]
$PhCH_2$	$PhCH_2$	**9**	**22**	70	22:78[h]
$PhCH_2$	H	**10**	**23**	74	80:20[d]
i-C_4H_9	PMB[f]	**11**	**24**	81	25:75[h]
i-C_4H_9	H	**12**	**25**	75	77:23[h]
c-$C_{10}H_{11}CH_2$	$PhCH_2$	**13**	**26**	71	17:83[h]
c-$C_{10}H_{11}CH_2$	H	**14**	**27**	79	83:17[g]

[a] All new reactions were carried out in CH_2Cl_2 at −20 to −30 °C; the reaction time was 20 h for R′ = H and 48 h for R′ ≠ H; desilylative workup was carried out with Bu_4NF in THF. [b] Isolated chemical yields of mixtures of *syn* and *anti* amino alcohols. [c] Ratios determined by ^1H NMR analysis of the crude mixture. [d] Reference 6. [e] Reference 12. [f] PMB = *p*-methoxybenzyl. [g] Reference 15. [h] See the Experimental Section. [i] Totally desilylated product.

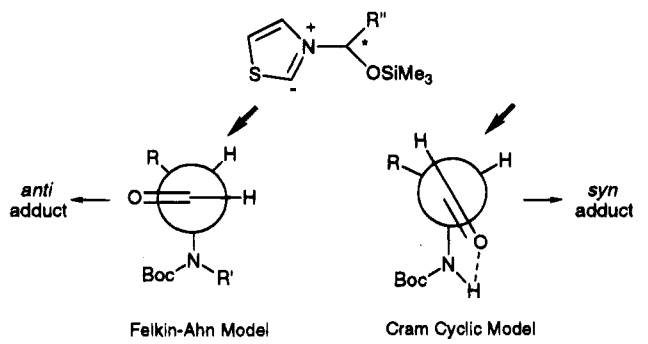
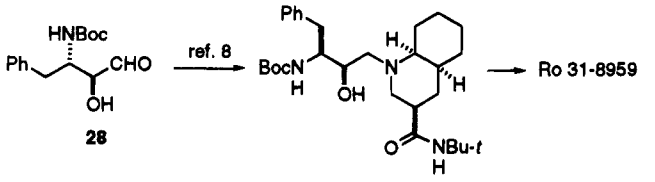


Figure 1. Conformational models of differentially protected α-amino aldehydes. Arrows indicate the side of addition of a thiazolium-2-ylide intermediate to the carbonyl according to the mechanism outlined for the reaction of 2-TST (**1**) with aldehydes (ref 18).

ratios.[16] Variation of the reactive aldehyde conformation as shown by the non-chelate Felkin–Anh[17] and proton-bridged Cram cyclic[18] models (Figure 1) provides a simple explanation for the *anti* and *syn* selectivity, respectively.[19] Owing to the ease of cleavage of the thiazole ring to the formyl group under almost neutral conditions,[20] adducts **15**–**27** can be considered as precursors to β-amino-α-hydroxy aldehydes. Hence, the overall procedure permits the conversion of each α-amino aldehyde into either of the two diastereomeric one-carbon higher homologues.

As an application of the foregoing results, we decided to examine the synthesis of the *N*-Boc-β-amino-α-hydroxy-4-phenylbutanal (**28**). This aldehyde has been recently considered by a Roche group[8] as a key intermediate for the preparation of the hydroxyethylamine isosteric dipeptide precursor to the potent and selective HIV protease inhibitor Ro 31-8959. Notwithstanding our previous work,[6] the synthesis of **28** was approached[8] by addition of **1** to the nitrogen singly protected *N*-Boc-L-phenylalaninal (**10**) (see eq 1 and Table 1), which in fact gave the β-amino alcohols *syn*-**23** and *anti*-**23** in a 3:2 ratio.[21] Because of the unfavorable yet low stereoselectivity and the difficult separation of *syn* and *anti* isomers **23**, the aldehyde **28** was obtained in rather poor yield. Consequently this route to Ro 31-8959 was abandoned. Given the importance of this potential drug,[22] we report below an efficient synthesis of **28** by employing a suitable doubly protected L-phenylalaninal derivative to achieve *anti* selectivity in the reaction with **1**.



Results of Table 1 indicated that *N*-Bn-*N*-Boc-L-phenylalaninal (**9**) was suited to reaction with **1** to give as major product the β-amino alcohol *anti*-**22** featuring the required *S* configuration at the hydroxyl-bearing carbon atom. However in view of the difficult removal of the *N*-benzyl group by hydrogenolysis because of catalyst poisoning by thiazole,[23] we decided to employ the PMB group which can be easily removed under oxidative conditions.[24] Thus, the *N*-Boc-*N*-PMB-L-phenylalaninal (**31**) was prepared in four steps from L-phenylalanine by a two stage reduction–oxidation sequence through the alcohols **29** and **30** (Scheme 1). The enantiomeric purity of **31** was determined to be ≥95% ee by Mosher ester analysis (^1H NMR) of the alcohol **30** obtained by $NaBH_4$ reduction.[25] Then, treatment of crude **31** with 2-TST (**1**) under the standard conditions of Table 1 followed by desilylation afforded the β-amino alcohols *anti*-**32** and *syn*-**32** in a 75:25 ratio and 87% overall yield. Conversion into oxazolidinones[14] confirmed the assigned stereochemistry of these products. Separation by flash chromatography gave pure *anti*-**32** in 64% and *syn*-**32** in 15% yields from the alcohol **30**.

Next we examined the removal of the PMB group from *anti*-**32** and the conversion to aldehyde. The first operation required the protection of the hydroxyl group since the reaction of cerium ammonium nitrate (CAN) with *anti*-**32** led to decomposition of the alcohol. Hence treatment of the *O*-acetyl derivative *anti*-**33** with CAN

(16) Pure diastereomeric β-amino alcohols were separated and characterized in four selected cases (see the Experimental Section).

(17) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(18) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245. For a recent overview and a computational evaluation of Cram's rule, see: Fleischer, J. M.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 490.

(19) A study of the mechanism of the reaction between aldehydes and 2-TST (**1**), a quite special organosilicon compound which does not require any added activator, suggests that the reaction proceeds through a thiazolium-2-ylide as an intermediate (Dondoni, A.; Douglas, A. W.; Shinkai, I. *J. Org. Chem.* **1993**, *58*, 3196). Accordingly, the configuration of the newly formed stereogenic center of the adduct should be determined in the step where the ylide attacks the aldehyde carbonyl.

(20) For overviews on the "thiazole aldehyde synthesis", see: (a) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, Switzerland, 1992; pp 377–437. (b) Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo, Japan, and VCH: Weinheim, Germany, 1992; pp 105–128.

(21) By contrast, *anti*-**23** and *syn*-**23** are formed in a 80:20 ratio by reduction (DIBALH–$ZnCl_2$) of the corresponding monoprotected *N*-Boc ketone. See ref 31 for tunable stereoselective reduction of amino ketones.

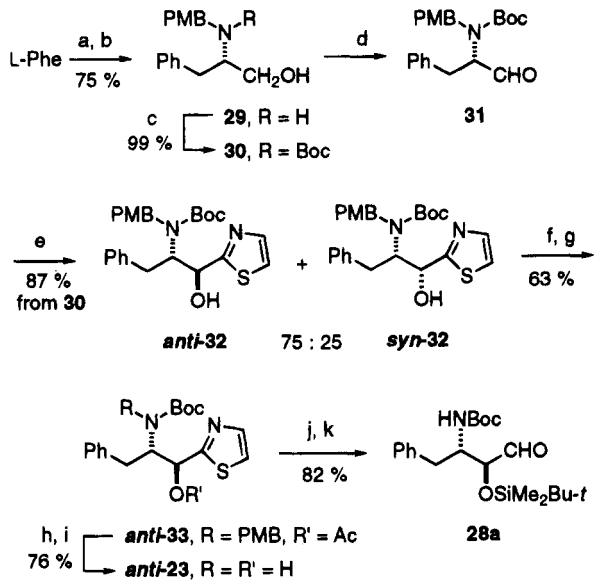
(22) *Drugs Future* **1995**, *20*, 321.

(23) Unsuccessful debenzylation of *O*-benzyl and *N*-benzyl derivatives bearing the thiazole ring by catalytic hydrogenolysis (H_2/Pd–C or $Pd(OH)_2$–C) was registered in several instances in our laboratory.

(24) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

(25) Racemic **31** was obtained when the precursor amino alcohol **29** was prepared from phenylalanine methyl ester by a different sequence, i.e., installation of the PMB group by reaction with *p*-methoxybenzyl aldehyde (Et_3N, toluene, reflux) and reduction ($LiAlH_4$, THF, 0 °C).

Scheme 1[a]



[a] Key: PBM = *p*-methoxybenzyl. (a) $LiAlH_4$, THF, reflux, 1 h; (b) 1. *p*-anisaldehyde, toluene, 90 °C, 1 h, 2. $NaBH_4$, MeOH, 0 °C, 30 min; (c) Boc_2O, dioxane, rt, 18 h; (d) DMSO, $(COCl)_2$, CH_2Cl_2, $EtN(i\text{-}Pr)_2$, −78 to −45 °C; (e) 1. 2-TST (**1**), CH_2Cl_2, −20 °C, 48 h, 2. $Bu_4NF{\cdot}3H_2O$, THF, rt, 1 h; (f) 64% *anti*-**32** and 15% *syn*-**32**, after separation (silica gel); (g) Ac_2O, DMAP, pyridine, rt, 18 h; (h) CAN, $MeCN-H_2O$ (4:1), rt, 18 h; (i) 30% MeONa, MeOH, rt, 15 min; (j) *t*-$BuMe_2SiCl$, DMAP, imidazole, DMF, rt, 18 h; (k) 1. $CF_3SO_3CH_3$, MeCN, rt, 15 min, 2. $NaBH_4$, MeOH, 0 °C to rt, 20 min, 3. $HgCl_2$, $MeCN-H_2O$ (10:1), rt, 15 min.

and deacetylation with sodium methoxide afforded *anti*-**23** whose melting point and ^1H NMR data were in good agreement with those reported by the Roche group.[8] Also the conversion of this compound to aldehyde required the protection of the hydroxyl group. Hence after protection of *anti*-**23** as the *O*-*tert*-butyldimethylsilyl (TBDMS) ether and then cleavage of the thiazole ring by the standard one-pot protocol involving *N*-methylation (TfOMe), reduction ($NaBH_4$) and hydrolysis ($HgCl_2-H_2O$) gave the *N*-Boc-*O*-TBDMS-β-amino-α-hydroxy aldehyde **28a** in 25% isolated overall yield from L-phenylalanine. In conclusion, an improved thiazole-based synthesis of the chiral 4-phenylbutanal **28** by the judicious choice of the *N*-protecting groups of the starting α-amino aldehyde **31** has been now reported. Therefore, the use of this aldehyde for the preparation of the hydroxyethylamine isosteric dipetide intermediate to Ro 31-8959 now becomes of interest.

Experimental Section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[26] and freshly distilled prior to use. Flash column chromatography[27] was performed on silica gel 60 (230−400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with alcoholic solutions of ninhydrin or sulfuric acid. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Improved synthesis of the aldehyde **2** and the syntheses of new aldehydes **4**, **6**, **7**, **9**, **11**−**13**, and **31** from the commercial α-amino acids or their esters are described below. 2-(Trimethylsilyl)thiazole (2-TST, **1**) was conveniently prepared[28] from 2-bromothiazole (Acros).

***N*-(*tert*-Butoxycarbonyl)-*N*,*O*-isopropylidene-L-serinal (2).** A solution of *N*-(*tert*-butoxycarbonyl)-*N*,*O*-isopropylidene-L-serine methyl ester[29] (1.0 g, 3.9 mmol) in THF (5 mL) was added dropwise to an ice-cold suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in THF (10 mL). After the addition was complete, the ice bath was removed and the stirring was continued at rt for an additional 10 min. The suspension was cooled again (ice bath) and carefully treated with 0.5 mL of pH 7 phosphate buffer. The mixture was stirred for 15 min; the white precipitate was filtered off through a pad of Celite. The clear solution was dried (Na_2SO_4) and concentrated to dryness and the residue purified by flash chromatography (7:3 cyclohexane−EtOAc) to give pure *N*-(*tert*-butoxycarbonyl)-*N*,*O*-isopropylidene-L-serinol (0.78 g, 93%): $[\alpha]_D$ −24.1° (*c* 1.4, $CHCl_3$); ^1H NMR (DMSO-d_6, 80 °C) δ 1.42 (s, 12 H), 1.47 (s, 3 H), 3.25 (ddd, 1 H, *J* = 5.5, 8.5, 11.0 Hz), 3.56 (ddd, 1 H, *J* = 4.8, 9.0, 11.0 Hz), 3.74−3.83 (m, 1 H), 3.87 (dd, 1 H, *J* = 1.1, 7.8 Hz), 3.92 (dd, 1 H, *J* = 2.5, 9.8 Hz) 4.58 (t, 1 H, *J* = 5.5 Hz).

To a cold (−78 °C) stirred solution of oxalyl chloride (0.37 mL, 4.5 mmol) in CH_2Cl_2 (22 mL) was added dimethyl sulfoxide (0.6 mL, 9.0 mmol), and after 5 min at −78 °C, the reaction mixture was allowed to warm to −60 °C over 30 min, whereupon a solution of the above L-serinol (0.7 g, 3.0 mmol) in CH_2Cl_2 (12 mL) was slowly added. The reaction mixture was warmed to −45 °C upon 30 min and stirred at this temperature for 5 min, and then diisopropylethylamine (3.1 mL, 18.0 mmol) was slowly added. After a further 5 min of stirring, the cooling bath was removed and the solution was allowed to warm to 0 °C. The reaction mixture was then poured into a mixture of 10 mL of 1 M HCl and 2 g of ice and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with pH 7 phosphate buffer (3 × 15 mL), dried (Na_2SO_4), and concentrated to give the aldehyde **2** (0.7 g, crude): ^1H NMR (DMSO-d_6, 120 °C) δ 1.42 (s, 9 H), 1.50 (s, 3 H), 1.55 (s, 3 H), 4.03 (dd, 1 H, *J* = 3.5, 9.0 Hz), 4.09 (dd, 1 H, *J* = 7.1, 9.0 Hz), 4.35 (ddd, 1 H, *J* = 2.0, 3.5, 7.1 Hz), 9.54 (d, 1 H, *J* = 2.0 Hz).

***N*-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-serinal (4).** To a solution of *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester[29] (2.0 g, 9.18 mmol) in DMF (25 mL) were added imidazole (1.38 g, 20.18 mmol) and *tert*-butyldiphenylsilyl chloride (2.77 g, 10.1 mmol) at rt. The solution was stirred for 24 h and then poured into saturated brine (25 mL) and extracted with cyclohexane (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness, and the residue was purified by flash chromatography (9:1 cyclohexane−Et_2O) to give pure *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-serine methyl ester (4.0 g, 95%): $[\alpha]_D$ +14.3° (*c* 1.9, $CHCl_3$); ^1H NMR δ 1.02 (s, 9 H), 1.45 (s, 9 H), 3.73 (s, 3 H), 3.88 (dd, 1 H, *J* = 2.7, 10.0 Hz), 4.05 (dd, 1 H, *J* = 2.7, 10.0 Hz), 4.39 (dt, 1 H, *J* = 2.7, 8.8 Hz), 5.42 (d, 1 H, *J* = 8.8 Hz), 7.31−7.42 (m, 6 H), 7.55−7.61 (m, 4 H); ^{13}C NMR δ 19.2, 26.6, 28.3, 52.2, 55.5, 64.6, 80.0, 127.7, 129.8, 132.8, 132.9, 135.4, 135.5, 155.3, 171.2.

A stirred solution of this ester (3.66 g, 8.0 mmol) in CH_2Cl_2 (25 mL) cooled to −78 °C was treated with a 1.5 M solution of DIBALH in toluene (10.7 mL, 16.0 mmol). The rate of addition was adjusted so as to keep the temperature of the solution below −65 °C. The reaction mixture was stirred at −78 °C for an additional 2 h, and then the reaction was slowly quenched with cold (−78 °C) MeOH (2 mL), while the temperature of the mixture was kept below −65 °C. The resulting white emulsion was slowly treated with an ice-cold saturated NH_4Cl solution (20 mL). After 10 min of stirring, the mixture was filtered, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give the aldehyde **4** (2.60 g, crude): ^1H NMR δ 1.05 (s, 9 H), 1.46 (s, 9 H), 4.04 (dd, 1 H, *J* = 3.8, 10.4 Hz), 4.21 (dd, 1 H, *J* = 3.4, 10.4 Hz), 4.34 (dt, 1 H, *J* = 3.6, 6.0 Hz), 5.48 (d, 1 H, *J* = 6.0 Hz), 7.35−7.49 (m, 6 H), 7.60−7.64 (m, 4 H), 9.68 (s, 1 H).

(26) Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Dondoni, A.; Merino, P. *Org. Synth.* **1993**, *72*, 21.
(29) Mckillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31.

***N*-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-threoninal (6).** *N*-(*tert*-Butoxycarbonyl)-L-threonine methyl ester[30] (2.14 g, 9.18 mmol) was processed as described above for *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester employed for the synthesis of the aldehyde **4**. The resulting *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-threonine methyl ester (3.98 g, 92%) showed the following data: $[\alpha]_D$ −4.6° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.07 (d, 3 H, *J* = 6.3 Hz), 1.10 (s, 9 H), 1.52 (s, 9 H), 3.62 (s, 3 H), 4.26 (dd, 1 H, *J* = 2.0, 10.1 Hz), 4.48 (dq, 1 H, *J* = 2.0, 6.4 Hz), 5.40 (d, 1 H, *J* = 10.1 Hz), 7.34−7.48 (m, 6 H), 7.62−7.71 (m, 4 H); ^{13}C NMR δ 19.1, 26.7, 26.8, 28.2, 52.0, 59.3, 70.2, 79.9, 127.4, 127.6, 129.7, 129.8, 132.8, 133.8, 135.7, 156.2, 171.5.

The reduction of this product (3.77 g, 8.0 mmol) with DIBALH (1.5 M solution, 10.7 mL, 16.0 mmol), as described above (see synthesis of **4**), gave the aldehyde **6** (2.75 g, crude): ^1H NMR δ 1.05 (d, 3 H, *J* = 6.4 Hz), 1.10 (s, 9 H), 1.50 (s, 9 H), 4.22 (dd, 1 H, *J* = 1.8, 9.2 Hz), 4.50 (dq, 1 H, *J* = 1.8, 6.4 Hz), 5.46 (d, 1 H, *J* = 9.2 Hz), 7.30−7.46 (m, 6 H), 7.60−7.68 (m, 4 H), 9.56 (s, 1 H).

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-L-phenylglycinal (7).** *N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-L-phenylglycine methyl ester[31] (1.0 g, 3.0 mmol) was reduced with DIBALH (1.5 M solution, 2.3 mL, 3.4 mmol) as described above (see synthesis of **4**) to give the aldehyde **7** (0.8 g, crude): ^1H NMR δ 1.40 (s, 9 H), 4.10−4.38 (m, 1 H), 4.58−5.0 (m, 2 H), 6.91−7.30 (m, 10 H), 9.66 (s, 1 H).

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-L-phenylalaninal (9).** *N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-L-phenylalanine methyl ester[31] (1.0 g, 2.7 mmol) was reduced with DIBALH (1.5 M solution, 2.1 mL, 3.1 mmol) as described above (see synthesis of **4**) to give the aldehyde **9** (0.85 g, crude): ^1H NMR (DMSO-d_6, 120 °C) δ 1.40 (s, 9 H), 2.99 (dd, 1 H, *J* = 5.1, 13.9 Hz), 3.27 (dd, 1 H, *J* = 5.4, 13.9 Hz), 3.78 (d, 1 H, *J* = 15.4 Hz), 4.01−4.10 (m, 1 H), 4.47 (d, 1 H, *J* = 15.4 Hz), 7.09−7.40 (m, 10 H), 9.47 (s, 1 H).

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-L-leucinal (11).** L-Leucine (Acros; 2.0 g, 15.2 mmol) was processed as described below for the preparation of the alcohol **30** to give the *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-L-leucinol derivative (3.18 g, 62%): $[\alpha]_D$ +7.8° (*c* 1.8, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.78 (d, 3 H, *J* = 6.2 Hz), 0.83 (d, 3 H, *J* = 6.2 Hz), 1.24−1.35 (m, 1 H), 1.37−1.53 (m, 2 H), 1.40 (s, 9 H), 3.33−3.52 (m, 2 H), 3.75 (s, 3 H), 3.83−3.94 (m, 1 H), 4.10 (t, 1 H, *J* = 4.9 Hz), 4.29 (s, 2 H), 6.86 (d, 2 H, *J* = 8.4 Hz), 7.23 (d, 2 H, *J* = 8.4 Hz).

Oxidation of this alcohol (1.0 g, 3.0 mmol) by the same procedure followed by the synthesis of the aldehyde **2** gave the aldehyde **11** (1.0 g, crude): ^1H NMR (DMSO-d_6, 120 °C) δ 0.84 (t, 6 H, *J* = 7.0 Hz), 1.40 (s, 9 H), 1.48−1.90 (m, 3 H), 3.76 (s, 3 H), 3.84 (dd, 1 H, *J* = 5.4, 8.0 Hz), 4.28 (d, 1H, *J* = 15.8 Hz), 4.55 (d, 1 H, *J* = 15.8 Hz), 6.90 (d, 2 H, *J* = 8.8 Hz), 7.25 (d, 2 H, *J* = 8.8 Hz), 9.39 (s, 1 H).

***N*-(*tert*-Butoxycarbonyl)-L-leucinal (12).** To a solution of L-leucine methyl ester hydrochloride (Acros; 1.0 g, 5.5 mmol) in saturated $NaHCO_3$ solution (20 mL) was added a solution of Boc_2O (1.2 g, 5.5 mmol) in dioxane (5 mL). The mixture was stirred at rt for 18 h, and then CH_2Cl_2 (10 mL) was added. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4); the solvent was removed under reduced pressure and the residue purified by flash chromatography (4:1 cyclohexane−Et_2O) to give pure *N*-(*tert*-butoxycarbonyl)-L-leucine methyl ester (1.25 g, 93%): $[\alpha]_D$ −11.6° (*c* 1.5, $CHCl_3$); ^1H NMR δ 0.92 (d, 3 H, *J* = 2.3 Hz), 0.95 (d, 3 H, *J* = 2.3 Hz), 1.43 (s, 9 H), 1.44−1.78 (m, 3 H), 3.71 (s, 3 H), 4.25−4.36 (m, 1 H), 4.91 (d, 1 H, *J* = 8.2 Hz); ^{13}C NMR δ 21.8, 22.7, 24.7, 27.3, 28.2, 41.7, 52.0, 79.7, 155.3, 173.9.

The reduction of this ester (1.0 g, 4.0 mmol) with DIBALH (1.5 M solution, 5.3 mL, 8.0 mmol), as described above (see synthesis of **4**), gave the aldehyde **12** (0.85 g, crude): ^1H NMR δ 0.85−1.10 (m, 6 H), 1.22−1.42 (m, 1 H), 1.43 (s, 9 H), 1.50−1.85 (m, 2 H), 4.19−4.30 (m, 1 H), 4.90−5.09 (m, 1 H), 9.58 (s, 1 H).

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-3-cyclohexyl-L-alaninal (13).** Thionyl chloride (0.96 g, 8.1 mmol) was added dropwise to a suspension of 3-cyclohexyl-L-alanine (Aldrich; 1.0 g, 5.8 mmol) in MeOH (5 mL) at 0 °C. The bath was removed, and the solution was stirred at rt for 48 h and concentrated to give 1.3 g of ester hydrochloride. A mixture of this ester (1.0 g, 4.5 mmol), Et_3N (0.7 mL, 4.9 mmol), PhCHO (0.5 mL, 4.9 mmol), and $MgSO_4$ (1.0 g) in CH_2Cl_2 (20 mL) was stirred at rt for 20 h and then filtered through Celite and concentrated. The residue was dissolved in MeOH (20 mL), cooled (ice bath), and treated with $NaBH_4$ (0.37 g, 9.8 mmol) under stirring. The solution was stirred at this temperature for 20 min, diluted with acetone (1 mL), and concentrated. The residue was partitioned between H_2O (20 mL) and EtOAc (3 × 10 mL). The organic extracts were dried (Na_2SO_4), and after evaporation of the solvent under reduced pressure, the residue was dissolved in dioxane (20 mL) and treated with Boc_2O (1.0 g, 4.9 mmol). After 18 h at rt, the solution was concentrated. Flash chromatography of the crude product (9:1 cyclohexane−Et_2O) gave pure *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-3-cyclohexyl-L-alanine methyl ester (1.37 g, 85%): $[\alpha]_D$ −66.0° (*c*, 0.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.74−0.90 (m, 2 H), 1.02−1.21 (m, 4 H), 1.40 (s, 9 H), 1.40−1.46 (m, 1 H), 1.52−1.67 (m, 5 H), 1.68−1.80 (m, 1 H), 3.57 (s, 3 H), 4.34−4.49 (m, 3 H), 7.20−7.35 (m, 5 H).

A solution of this compound (1.0 g, 2.8 mmol) in THF (5 mL) was added dropwise to an ice-cold suspension of $LiAlH_4$ (0.16 g, 4.2 mmol) in THF (10 mL). After the addition was complete, the ice bath was removed and the stirring was continued for an additional 10 min; then the suspension was cooled again (ice bath) and carefully treated with 0.5 mL of pH 7 phosphate buffer. The mixture was stirred for 15 min, and the white precipitate was filtered off through a pad of Celite. The clear solution was dried (Na_2SO_4) and concentrated to dryness and the residue purified by flash chromatography (4:1 cyclohexane−EtOAc) to give pure *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-3-cyclohexyl-L-alaninol (0.86 g, 93%): $[\alpha]_D$ −2.1° (*c* 0.6, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 0.71−0.93 (m, 2 H), 1.02−1.23 (m, 4 H), 1.24−1.50 (m, 3 H), 1.40 (s, 9 H), 1.51−1.77 (m, 4 H), 3.34−3.43 (m, 1 H), 3.44−3.54 (m, 1 H), 3.90−4.01 (m, 1 H), 4.13 (t, 1 H, *J* = 5.0 Hz), 4.35 (s, 2 H), 7.15−7.38 (m, 5 H).

The oxidation of this alcohol (0.7 g, 2.1 mmol) by the procedure described above for the synthesis of **2** gave the aldehyde **13** (0.7 g, crude): ^1H NMR (DMSO-d_6, 120 °C) δ 0.75−1.0 (m, 2 H), 1.02−1.36 (m, 5 H), 1.41 (s, 9 H), 1.44−1.83 (m, 6 H), 3.92 (dd, 1 H, *J* = 5.0, 8.1 Hz), 4.30 (d, 1 H, *J* = 16.0 Hz), 4.55 (d, 1 H, *J* = 16.0 Hz), 7.20−7.38 (m, 5 H), 9.43 (s, 1 H).

Addition of 2-(Trimethylsilyl)thiazole (2-TST, 1) to α-Amino Aldehydes 2−13. To a cold (−20 °C) stirred solution of freshly prepared aldehyde (4 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of 2-TST (**1**) (4.6 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stand at −20 °C for 20 h in the case of *N*-monoprotected α-amino aldehydes and for 48 h in the case of *N*,*N*-diprotected α-amino aldehydes. The solvent was then evaporated under reduced pressure; the residue was dissolved in THF (20 mL) and treated under stirring with $Bu_4NF·3H_2O$ (Acros; 4.6 mmol). The solution was stirred at rt for 1 h and then concentrated. The crude syrup was partitioned between H_2O (20 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a mixture of diastereomeric alcohols whose ratio was determined by ^1H NMR. The overall yield of *syn* and *anti* amino alcohols was determined after filtration of their crude mixture through a short column of silica gel. Examples of separations of *syn* and *anti* isomers are reported for compounds **15**, **17**, **19**, and **22**.

***Syn* and *anti* amino alcohols 15:** 85% overall yield based on the amino alcohol after filtration through silica gel (1:1 cyclohexane−EtOAc); ^1H-NMR (DMSO-d_6, 120 °C, ds_{anti} 92%) δ 1.38 (s, 0.72 H), 1.40 (s, 8.52 H), 1.47 (s, 2.76 H), 1.48 (s, 0.24 H), 1.57 (s, 2.76 H), 3.82 (dd, 0.92 H, *J* = 6.5, 8.8 Hz), 3.89−3.95 (m, 0.08 H), 3.98 (dd, 0.92 H, *J* = 2.8, 8.8 Hz), 4.15−4.22 (m, 0.16 H), 4.25 (ddd, 0.92 H, *J* = 2.8, 4.1, 6.5 Hz), 5.15 (d, 0.92 H, *J* = 4.1 Hz), 5.26 (d, 0.08 H, *J* = 5.7 Hz), 7.48−7.57 (m, 1 H), 7.67−7.74 (m, 1 H).

Recrystallization of this mixture from cyclohexane gave pure *anti*-**15** (66% overall yield from the amino alcohol) as a white solid: mp 170−172 °C; $[\alpha]_D$ −53.4° (*c* 0.7, $CHCl_3$); ^1H-NMR (DMSO-d_6, 120 °C) δ 1.40 (s, 9 H), 1.47 (s, 3 H), 1.57 (s, 9 H), 3.82 (dd, 1 H, *J* = 6.5, 8.8 Hz), 3.98 (dd, 1 H, *J* = 2.8, 8.8 Hz), 4.25 (ddd, 1 H, *J* = 2.8, 4.1, 6.5 Hz), 5.15 (d, 1 H, *J* = 4.1 Hz), 7.52 (d, 1 H, *J* = 3.1 Hz), 7.70 (d, 1 H, *J* = 3.1 Hz). Anal. Calcd

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for $C_{14}H_{22}N_2O_4S$: C, 53.97; H, 7.05; N, 8.91. Found: C, 54.09; H, 7.16; N, 9.01.

***Syn* and *anti* amino alcohols 17:** 51% overall yield based on the amino ester after filtration through silica gel (20:1 Et_2O–MeOH); ^1H NMR ($CDCl_3 + D_2O$, 55 °C, ds_{syn} 75%) δ 1.34 (s, 2.25 H), 1.38 (s, 6.75 H), 3.68–3.82 (m, 1.75 H), 3.95–4.08 (m, 1.25 H), 5.14 (d, 0.25 H, J = 3.2 Hz), 5.29 (d, 0.75 H, J = 4.8 Hz), 7.29–7.31 (m, 1 H), 7.69–7.71 (m, 1 H).

Chromatography on silica gel of the mixture (40:1 Et_2O–MeOH) gave first the totally desilylated *anti*-**17** (13% overall yield from the amino ester) as a syrup: $[\alpha]_D$ −66.9° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3 + D_2O$) δ 1.34 (s, 9 H), 3.70 (dd, 1 H, J = 4.6, 11.9 Hz), 3.95–4.08 (m, 2 H), 5.12 (d, 1 H, J = 3.5 Hz), 5.60 (bs, 1 H), 7.31 (d, 1 H, J = 3.2 Hz), 7.68 (d, 1 H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3 + D_2O$) δ 27.9, 56.4, 62.2, 75.8, 80.5, 119.7, 142.6, 158.1, 175.8. Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.17; H, 6.61; N, 10.21. Found: C, 48.35; H, 6.40; N, 9.89.

Eluted second was the totally desilylated *syn*-**17** (38% overall yield from the amino ester) as a white solid: mp 155–156 °C; $[\alpha]_D$ −2.5° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3 + D_2O$) δ 1.38 (s, 9 H), 3.67 (dd, 1 H, J = 6.4, 11.8 Hz), 3.80 (dd, 1 H, J = 4.1, 11.8 Hz), 4.00 (m, 1 H), 5.28 (d, 1 H, J = 4.0 Hz), 5.52 (d, 1 H, J = 8.5 Hz), 7.30 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3 + D_2O$) δ 28.0, 56.5, 62.2, 71.7, 80.1, 119.5, 142.6, 163.2, 174.4. Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.17; H, 6.61; N, 10.21. Found: C, 47.92; H, 6.37; N, 9.94.

***Syn* and *anti* amino alcohols 19:** 60% overall yield based on the amino ester after filtration through silica gel (20:1 Et_2O–MeOH); ^1H NMR ($CDCl_3 + D_2O$, 55 °C, ds_{syn} 78%) δ 1.23 (d, 2.34 H, J = 6.4 Hz), 1.28 (d, 0.66 H, J = 6.4 Hz), 1.39 (s, 7 H), 1.40 (s, 2 H), 3.75–3.80 (m, 0.78 H), 3.86–4.25 (m, 1 H), 4.39 (dq, 0.22 H, J = 1.9, 6.4 Hz), 5.15 (d, 0.22 H, J = 2.6 Hz), 5.28 (d, 0.78 H, J = 4.9 Hz), 7.30–7.32 (m, 1 H), 7.60–7.70 (m, 1 H).

Chromatography on silica gel of the mixture (40:1 Et_2O–MeOH) gave first the totally desilylated *anti*-**19** (13% overall yield from the amino ester) as a syrup: $[\alpha]_D$ −110.4° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3 + D_2O$) δ 1.28 (d, 3 H, J = 6.4 Hz), 1.40 (s, 9 H), 3.95–4.08 (m, 1 H), 4.36 (m, 1 H), 5.14 (d, 1 H, J = 3.2 Hz), 5.63 (bs, 1 H), 7.30 (d, 1 H, J = 3.2 Hz), 7.74 (d, 1 H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3 + D_2O$) δ 20.8, 27.9, 60.1, 66.8, 77.7, 80.8, 119.7, 142.7, 159.1, 176.4. Anal. Calcd for $C_{12}H_{20}N_2O_4S$: C, 49.98; H, 6.98; N, 9.72. Found: C, 50.24; H, 7.10; N, 9.98.

Eluted next was the totally desilylated *syn*-**19** (47% overall yield from the amino ester) as a syrup: $[\alpha]_D$ +7.8° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3 + D_2O$) δ 1.23 (d, 3 H, J = 6.4 Hz), 1.39 (s, 9 H), 3.75–3.80 (m, 1 H), 4.17–4.21 (m, 1 H), 5.29 (d, 1 H, J = 4.8 Hz), 5.50 (d, 1 H, J = 9.3 Hz), 7.32 (d, 1 H, J = 3.2 Hz), 7.61 (d, 1 H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3 + D_2O$) δ 19.5, 27.8, 59.4, 68.0, 74.6, 79.9, 119.4, 142.1, 157.4, 172.6. Anal. Calcd for $C_{12}H_{20}N_2O_4S$: C, 49.98; H, 6.98; N, 9.72. Found: C, 50.12; H, 7.23; N, 9.46.

***Syn* and *anti* amino alcohols 20:** 67% overall yield based on the amino ester after filtration through silica gel (3:2 cyclohexane–EtOAc); ^1H NMR (DMSO-d_6, 120 °C, ds_{anti} 60%) δ 1.24 (s, 3.6 H), 1.35 (s, 5.4 H), 4.32 (d, 0.4 H, J = 15.1 Hz), 4.39 (s, 0.6 H), 4.40 (d, 0.4 H, J = 15.1 Hz), 5.04 (t, 0.4 H, J = 6.8 Hz), 5.36 (d, 0.6 H, J = 7.8 Hz), 5.51 (d, 0.4 H, J = 7.4 Hz), 5.68 (d, 0.6 H, J = 7.8 Hz), 6.08 (bs, 1 H, ex D_2O), 6.82–7.45 (m, 10 H), 7.49 (d, 0.4 H, J = 3.2 Hz), 7.54 (d, 0.6 H, J = 3.2 Hz), 7.61 (d, 0.4 H, J = 3.2 Hz), 7.71 (d, 0.6 H, J = 3.2 Hz).

***Syn* and *anti* amino alcohols 22:** 70% overall yield based on the amino ester after filtration through silica gel (3:2 cyclohexane–EtOAc); ^1H NMR (ds_{anti} 78%) δ 1.42 (s, 1.98 H), 1.49 (s, 7.02 H), 2.60 (dd, 0.78 H, J = 3.2, 13.5 Hz), 2.76 (dd, 0.22 H, J = 5.9, 12.9 Hz), 3.22–3.60 (m, 2 H), 3.95 (bs, 0.22 H), 4.14–4.35 (m, 2 H), 4.96 (dd, 0.22 H, J = 4.9, 8.4 Hz), 5.26 (bs, 0.78 H), 6.64 (bs, 0.78 H), 6.95–7.40 (m, 11 H), 7.65 (d, 0.22 H, J = 3.2 Hz), 7.77 (d, 0.78 H, J = 3.2 Hz).

Chromatography on silica gel of the mixture (100:4.5 CH_2Cl_2–EtOAc) gave first *anti*-**22** (53% overall yield from the amino ester) as a syrup: $[\alpha]_D$ +20.4° (*c* 1.2, $CHCl_3$); ^1H NMR δ 1.49 (s, 9 H), 2.60 (dd, 1 H, J = 3.2, 13.5 Hz), 3.41 (dd, 1 H, J = 11.0, 13.5 Hz), 3.49 (d, 1 H, J = 15.7 Hz), 4.18 (dd, 1 H, J = 3.2, 11.0 Hz), 4.28 (d, 1 H, J = 15.7 Hz), 5.26 (bs, 1 H), 6.64 (bs, 1 H), 7.03–7.11 (m, 4 H), 7.12–7.29 (m, 6 H), 7.30 (d, 1 H, J = 3.2 Hz), 7.77 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 28.1, 30.8, 55.5, 69.3, 76.1, 81.4, 119.4, 126.5, 127.5, 127.8, 128.7, 129.5, 138.2, 139.3, 143.0, 158.3, 174.2. Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.91; H, 6.65; N, 6.60. Found: C, 68.23; H, 6.93; N, 6.76.

Eluted next was *syn*-**22** (15% overall yield from the amino ester) as a syrup: $[\alpha]_D$ +18.1° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.42 (s, 9 H), 2.76 (dd, 1 H, J = 5.9, 12.9 Hz), 3.43 (dd, 1 H, J = 8.9, 12.9 Hz), 3.52 (d, 1 H, J = 15.1 Hz), 3.93 (ddd, 1 H, J = 4.9, 5.9, 8.9 Hz), 4.26 (d, 1 H, J = 15.1 Hz), 4.96 (dd, 1 H, J = 4.9, 8.4 Hz), 6.95–7.09 (m, 4 H), 7.10–7.30 (m, 7 H), 7.22 (bs, 1 H, ex D_2O), 7.65 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 28.1, 35.2, 55.3, 67.0, 73.2, 81.7, 118.8, 126.8, 127.7, 128.6, 128.8, 129.7, 137.9, 138.5, 143.0, 158.5, 177.3. Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.91; H, 6.65; N, 6.60. Found: C, 68.06; H, 6.71; N, 6.74.

***Syn* and *anti* amino alcohols 24:** 81% overall yield based on the amino alcohol after filtration through silica gel (3:2 cyclohexane–EtOAc); ^1H NMR (DMSO-d_6, 120 °C, ds_{anti} 75%) δ 0.63 (d, 3 H, J = 6.0 Hz), 0.69 (d, 0.25 H, J = 6.0 Hz), 0.72 (d, 0.75 H, J = 6.0 Hz), 1.12–1.70 (m, 3 H), 1.36 (s, 6.75 H), 1.44 (s, 2.25 H), 3.94 (s, 3 H), 4.20–4.42 (m, 3 H), 4.95–5.05 (m, 1 H), 5.84 (d, 0.25 H, J = 5.0 Hz), 5.92 (d, 0.75 H, J = 5.6 Hz), 6.80–6.88 (m, 2 H), 7.14–7.24 (m, 2 H), 7.52 (d, 0.75 H, J = 3.2 Hz), 7.56 (d, 0.25 H, J = 3.2 Hz), 7.70 (d, 0.75 H, J = 3.2 Hz), 7.71 (d, 0.25 H, J = 3.2 Hz).

***Syn* and *anti* amino alcohols 25:** 75% overall yield based on the amino ester after filtration through silica gel (1:1 cyclohexane–EtOAc); ^1H NMR (DMSO-d_6, 120 °C, ds_{anti} 77%) δ 0.80 (d, 0.69 H, J = 6.6 Hz), 0.85 (d, 0.69 H, J = 6.6 Hz), 0.90 (d, 4.62 H, J = 6.6 Hz), 1.10–1.75 (m, 3 H), 1.46 (s, 6.93 H), 1.50 (s, 2.07 H), 3.85–4.06 (m, 1 H), 4.80–4.90 (m, 1 H), 5.64–5.95 (m, 2 H), 7.51 (d, 1 H, J = 3.2 Hz), 7.72 (d, 1 H, J = 3.2 Hz).

***Syn* and *anti* amino alcohols 26:** 71% overall yield based on the amino alcohol after filtration through silica gel (3:2 cyclohexane–EtOAc); ^1H NMR (DMSO-d_6, 120 °C, ds_{anti} 83%) δ 0.58–0.79 (m, 2 H), 0.92–1.30 (m, 5 H), 1.34 (s, 7.47 H), 1.37 (s, 1.53 H), 1.38–1.70 (m, 6 H), 4.26–4.50 (m, 3 H), 4.96–5.07 (m, 1 H), 5.88–6.00 (m, 1 H), 7.16–7.32 (m, 5 H), 7.54 (d, 0.83 H, J = 3.2 Hz), 7.57 (d, 0.17 H, J = 3.2 Hz), 7.71 (d, 1 H, J = 3.2 Hz).

***N*-(4-Methoxybenzyl)-L-phenylalaninol (29).** L-Phenylalanine (Acros; 2.0 g, 12.1 mmol) was carefully added portionwise from the top of the condenser to a stirred and refluxed mixture of $LiAlH_4$ (1.01 g, 26.6 mmol) in THF (40 mL). After the addition was complete, the mixture was refluxed for an additional 1 h and then cooled to rt and slowly treated with 1.5 mL of 5 M KOH solution. The mixture was stirred for 20 min, and then, the white precipitate was filtered off through a pad of Celite. The pale yellow solution was dried (Na_2SO_4) and the solvent removed under reduced pressure. To the crude product dissolved in toluene (30 mL) were added *p*-anisaldehyde (1.65 g, 12.1 mmol) and activated 4 Å powdered molecular sieves (1.21 g). The suspension was stirred for 1 h at 90 °C and concentrated to dryness. The residue was dissolved in MeOH (30 mL), cooled (0 °C), and treated with $NaBH_4$ (0.69 g, 18.15 mmol). The mixture was stirred for 30 min at 0 °C, diluted with acetone (5 mL), filtered through Celite, and concentrated. The crude residue was washed with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow solid. Recrystallization of this material from cyclohexane–Et_2O gave the amino alcohol **29** (2.46 g, 75%) as a pure white solid: mp 85–86 °C; $[\alpha]_D$ −10.3° (*c* 0.6, $CHCl_3$); ^1H NMR δ 2.0–2.25 (m, 2 H), 2.76 (dd, 1 H, J = 7.0, 13.2 Hz), 2.83 (dd, 1 H, J = 7.0, 13.2 Hz), 2.92–3.02 (m, 1 H), 3.35 (dd, 1 H, J = 5.2, 10.8 Hz), 3.65 (dd, 1 H, J = 3.8, 10.8 Hz), 3.73 (s, 2 H), 3.80 (s, 3 H), 6.81–6.89 (m, 2 H), 7.11–7.35 (m, 7 H); ^{13}C NMR δ 37.8, 50.4, 55.1, 59.1, 62.3, 113.7, 126.2, 128.4, 129.1, 131.9, 138.4, 158.5. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.31; H, 7.93; N, 5.20.

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-L-phenylalaninol (30).** To a stirred solution of **29** (1.5 g, 5.53 mmol) in dioxane (10 mL) was added Boc_2O (1.45 g, 6.63 mmol) at rt. After being stirred for 18 h at this temperature, the solution was concentrated. Chromatography of the residue on silica gel (3:1 cyclohexane–EtOAc) gave pure **30** (2.4 g, 99%) as a syrup: $[\alpha]_D$ −43.0° (*c* 1.2, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.38 (s, 9 H), 2.76–2.88 (m, 2 H), 3.38–3.61 (m, 2 H), 3.74 (s, 3 H), 3.92–4.03 (m, 1 H), 4.15 (d, 1 H, J = 15.1 Hz), 4.20–4.28 (m, 1 H, ex D_2O), 4.27 (d, 1 H, J = 15.1 Hz), 6.78–6.85 (m, 2 H), 7.07–

7.27 (m, 7 H). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.28; H, 7.70; N, 3.74.

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-L-phenylalaninal (31).** To a cold (−78 °C) stirred solution of oxalyl chloride (0.33 mL, 4.0 mmol) in CH_2Cl_2 (20 mL) was added dimethyl sulfoxide (0.5 mL, 8.1 mmol), and after 5 min at −78 °C, the reaction mixture was allowed to warm to −60 °C over 30 min, whereupon a solution of the alcohol **30** (1.0 g, 2.7 mmol) in CH_2Cl_2 (11 mL) was slowly added. The reaction mixture was warmed to −45 °C upon 30 min and stirred at this temperature for 5 min, and then diisopropylethylamine (2.3 mL, 16.2 mmol) was slowly added. After a further 5 min of stirring, the cooling bath was removed and the solution was allowed to warm to 0 °C. The reaction mixture was then poured into a mixture of 10 mL of 1 M HCl and 2 g of ice and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with pH 7 phosphate buffer (3 × 15 mL), dried (Na_2SO_4), and concentrated to give the aldehyde **31** (1.0 g, crude) as a syrup which was immediately utilized without further purification: ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.42 (s, 9 H), 2.95 (dd, 1 H, J = 8.8, 13.5 Hz), 3.26 (dd, 1 H, J = 5.4, 13.5 Hz), 3.74 (d, 1 H, J =15.5 Hz), 3.75 (s, 3 H), 3.99 (dd, 1 H, J = 5.4, 8.8 Hz), 4.41 (d, 1 H, J = 15.5 Hz), 6.82−6.90 (m, 2 H), 7.08−7.34 (m, 7 H), 9.44 (s, 1 H).

(*S,S*)- and (1*R*,2*S*)-2-[2-[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)amino]-1-hydroxy-3-phenylpropyl]-1,3-thiazole (*anti*- and *syn*-32). To a cold (−20 °C) stirred solution of freshly prepared aldehyde **31** (1.0 g) in CH_2Cl_2 (8 mL) was added a solution of 2-TST (**1**) (0.51 g, 3.2 mmol) in CH_2Cl_2 (8 mL) dropwise. The reaction mixture was allowed to stand at −20 °C for 48 h and then concentrated under reduced pressure. The residue was dissolved in THF (15 mL) and treated under stirring with $Bu_4NF{\cdot}3H_2O$ (1.0 g, 3.2 mmol). After being stirred for 1 h at rt, the solution was concentrated. ^{1}H NMR analysis of the crude product showed a 75:25 mixture of *anti*/*syn* diastereomers. Chromatography on silica gel (9:1 toluene−Et_2O) of this mixture gave first pure *anti*-**32** (0.78 g, 64% from **30**) as a syrup: $[\alpha]_D$ = +33.6° (*c* 1.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.32 (s, 9 H), 3.06 (d, 2 H, J = 7.1 Hz), 3.72 (s, 3 H), 4.01 (d, 1 H, J = 15.3 Hz), 4.10 (d, 1 H, J = 15.3 Hz), 4.30−4.42 (m, 1 H), 5.19 (dd, 1 H, J = 4.1, 6.5 Hz), 6.08 (d, 1 H, J = 4.1 Hz, ex D_2O), 6.63−6.71 (m, 2 H), 6.81−6.90 (m, 2 H), 6.96−7.03 (m, 2 H), 7.07−7.19 (m, 3 H), 7.53 (d, 1 H, J = 3.2 Hz), 7.71 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16. Found: C, 66.23; H, 6.84; N, 6.05.

Eluted second was additional *anti*-**32** contaminated by *syn*-**32** (98 mg, 8% from **30**). Eluted next was pure *syn*-**32** (0.18 g, 15% from **30**) as a syrup: $[\alpha]_D$ = +4.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.33 (s, 9 H), 2.94 (d, 2 H, J = 7.5 Hz), 3.74 (s, 3 H), 4.24 (d, 1 H, J = 16.0 Hz), 4.34−4.44 (m, 1 H), 4.37 (d, 1 H, J = 16.0 Hz), 5.07 (dd, 1 H, J = 5.5, 7.5 Hz), 6.05 (d, 1 H, J = 5.5 Hz, ex D_2O), 6.70−6.78 (m, 2 H), 6.96−7.08 (m, 4 H), 7.10−7.20 (m, 3 H), 7.55 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16. Found: C, 66.31; H, 6.38; N, 6.35.

(*S,S*)-2-[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-amino]-3-phenyl-1-(1,3-thiazol-2-yl)propyl Acetate (*anti*-33). To a stirred solution of *anti*-**32** (0.70 g, 1.54 mmol) in pyridine (4 mL) were added Ac_2O (0.22 mL, 2.31 mmol) and DMAP (catalytic) at rt. After being stirred for 18 h, the solution was concentrated. Chromatography of the crude residue on silica gel (3:2 cyclohexane−EtOAc) afforded pure *anti*-**33** (0.75 g, 99%) as a syrup: $[\alpha]_D$ = −34.8° (*c* 1.2, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.36 (s, 9 H), 1.95 (s, 3 H), 3.05 (dd, 1 H, J = 6.1, 14.6 Hz), 3.10 (dd, 1 H, J = 5.5, 14.6 Hz), 3.73 (s, 3 H), 3.91 (d, 1 H, J = 15.3 Hz), 4.04 (d, 1 H, J = 15.3 Hz), 4.40−4.52 (m, 1 H), 6.41 (d, 1 H, J = 7.1 Hz), 6.62−6.73 (m, 2 H), 6.79−6.88 (m, 2 H), 6.98−7.10 (m, 2 H), 7.12−7.25 (m, 3 H), 7.63 (d, 1 H, J = 3.2 Hz), 7.76 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N, 5.64. Found: C, 65.41; H, 6.32; N, 5.83.

(*S,S*)-2-[2-[*N*-(*tert*-Butoxycarbonyl)amino]-1-hydroxy-3-phenylpropyl]-1,3-thiazole (*anti*-23). To a solution of *anti*-**33** (0.50 g, 1.0 mmol) in 14.7 mL of MeCN−H_2O (4:1) at rt was added ceric ammonium nitrate (CAN; 1.64 g, 3.0 mmol). The reaction mixture was vigorously stirred at rt for 18 h, neutralized with Et_3N (1−2 drops), and concentrated to dryness. The residue was partitioned between H_2O (20 mL) and EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (7:3 cyclohexane−EtOAc) to remove *p*-anisaldehyde gave the crude *N*-(*tert*-butoxycarbonyl)amino derivative of *anti*-**33** which was dissolved in MeOH (2 mL) and treated with 30% NaOMe solution (1 mL). After being stirred for 15 min at rt, the solution was neutralized with AcOH (1−2 drops) and concentrated. Chromatography of the crude residue on silica gel (3:2 cyclohexane−EtOAc) afforded the amino alcohol *anti*-**23** (0.25 g, 76% from *anti*-**33**) as a white solid: mp 118−119 °C (lit.[8] mp 112−120 °C); $[\alpha]_D$ = −45.2° (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 1.38 (s, 9 H), 2.85−3.05 (m, 2 H), 4.23−4.35 (m, 1 H), 4.88 (d, 1 H, J = 5.8 Hz), 5.12 (bs, 1 H), 5.30 (bs, 1 H), 7.14−7.32 (m, 5 H), 7.36 (d, 1 H, J = 3.2 Hz), 7.81 (d, 1 H, J = 3.2 Hz); ^{13}C NMR δ 28.2, 35.5, 58.0, 74.2, 80.2, 119.3, 126.5, 128.5, 129.3, 137.8, 142.5, 157.1, 172.9. Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38. Found: C, 61.23; H, 6.35; N, 8.39.

(*S,S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanal (28a). To a stirred solution of *anti*-**23** (0.21 g, 0.63 mmol) in dry DMF (3 mL) were added imidazole (85 mg, 1.26 mmol), DMAP (catalytic), and *tert*-butyldimethylsilyl chloride (0.14 g, 0.94 mmol). After stirring for 18 h at rt, the solution was diluted with MeOH (3 mL), stirred at rt for an additional 1 h, and then concentrated. The residue was treated with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude syrup which was purified by flash chromatography on silica gel (4:1 cyclohexane−Et_2O) to give the *O*-*tert*-butyldimethylsilyl derivative (0.27 g, 96%). A mixture of this compound (0.25 g, 0.56 mmol), activated 4 Å powdered molecular sieves (1.11 g), and anhydrous MeCN (6 mL) was stirred at rt for 10 min, and then methyl triflate (68 μL, 0.67 mmol) was added. The suspension was stirred for 15 min and concentrated to dryness. The residue was suspended in MeOH (6 mL), cooled to 0 °C, and treated with $NaBH_4$ (47 mg, 1.23 mmol). The mixture was stirred at rt for 20 min, diluted with acetone (0.5 mL), filtered through Celite, and concentrated. The residue was dissolved in 10:1 MeCN−H_2O (6 mL) and the solution treated with $HgCl_2$ (0.15 g, 0.56 mmol) in 0.5 mL of the same solvent mixture. The mixture was stirred for 15 min and then filtered through Celite and concentrated (bath temperature not exceeding 40 °C). The residue was dissolved in CH_2Cl_2 (6 mL) and washed with 20% aqueous KI (10 mL), and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and quickly filtered through a pad of Florisil to give crude **28a** as a clear yellow syrup (0.19 g, 85% crude yield, 95% pure by ^{1}H NMR analysis). An analytically pure sample of **28a** was obtained by flash chromatography on silica gel (9:1 cyclohexane−EtOAc) as a clear yellow solid: mp 95−96 °C; $[\alpha]_D$ = −31.4° (*c* 1.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.09 (s, 3 H), 0.13 (s, 3 H), 0.95 (s, 9 H), 1.31 (s, 9 H), 2.72 (dd, 1 H, J = 9.6, 13.7 Hz), 2.89 (dd, 1 H, J = 4.1, 13.7 Hz), 3.98 (dddd, 1 H, J = 4.1, 5.5, 8.2, 9.6 Hz), 4.13 (dd, 1 H, J = 1.4, 5.5 Hz), 6.28 (d, 1 H, J = 8.2 Hz), 7.10−7.32 (m, 5 H), 9.48 (d, 1 H, J = 1.4 Hz). Anal. Calcd for $C_{21}H_{35}NO_4Si$: C, 64.08; H, 8.96; N, 3.56. Found: C, 64.15; H, 9.21; N, 3.24.

Determination of the Configurational Stability of the α-Amino Aldehyde 31: Reduction of the Aldehyde 31 to the Alcohol 30. An ice-cold solution of freshly prepared aldehyde **31** (0.10 g) in MeOH (5 mL) was treated with $NaBH_4$ (23.0 mg, 0.59 mmol). After stirring for 30 min at the same temperature, TLC (3:1 cyclohexane−EtOAc) showed the formation of the alcohol **30**. The cold solution was diluted with acetone (1−2 drops) and concentrated to dryness. The residue was partitioned between saturated $NaHCO_3$ solution (10 mL) and EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 cyclohexane−EtOAc) of the residue afforded pure **30** (83 mg) as a syrup: $[\alpha]_D$ = −43.1° (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.37; H, 7.53; N, 3.49.

Esterification of 30 with (*R*)-(+)-MTPA. To a solution of the above alcohol **30** (20 mg, 0.05 mmol), DCC (11.6 mg, 0.06 mmol), and DMAP (a crystal) in dry CH_2Cl_2 (0.5 mL) was added (*R*)-(+)-MTPA (13.7 mg, 0.06 mmol). The mixture was stirred at rt for 12 h, filtered to remove the *N*,*N*′-dicyclohexylurea, and partitioned with EtOAc (2 × 5 mL) and H_2O (5 mL). The

combined organic layers were washed with 5 mL each of 1 M HCl, H_2O, saturated $NaHCO_3$ solution, and brine and then dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica gel (9:1 cyclohexane–EtOAc) gave the (*R*)-MTPA ester of **30** (25 mg, 85%): ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.36 (s, 9 H), 2.81 (dd, 1 H, J = 6.7, 14.8 Hz), 2.89 (dd, 1 H, J = 7.4, 14.8 Hz), 3.44 (s, 3 H), 3.74 (s, 3 H), 4.09 (d, 1 H, J = 16.3 Hz), 4.16 (d, 1 H, J = 16.3 Hz), 4.20–4.31 (m, 1 H), 4.35 (dd, 1 H, J = 5.2, 11.1 Hz), 4.52 (dd, 1 H, J = 7.7, 11.1 Hz), 6.74–6.82 (m, 2 H), 7.0–7.14 (m, 4 H), 7.15–7.30 (m, 3 H), 7.48 (s, 5 H).

The same procedure was followed with racemic[25] **30** to give the diastereomeric mixture of (*R*)-MTPA esters: ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.36 (s, 4.5 H), 1.37 (s, 4.5 H), 2.77–2.96 (m, 2 H), 3.43 (s, 1.5 H), 3.44 (s, 1.5 H), 3.74 (s, 3 H), 4.06–4.31 (m, 3 H), 4.32–4.41 (m, 1 H), 4.46–4.56 (m, 1 H), 6.74–6.82 (m, 2 H), 7.0–7.14 (m, 4 H), 7.15–7.30 (m, 3 H), 7.48 (s, 5 H).

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